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Mch3, a novel human apoptotic cysteine protease highly related to CPP32.

Fernandes-Alnemri T, Takahashi A, Armstrong R, Krebs J, Fritz L, Tomaselli KJ, Wang L, Yu Z, Croce CM, Salveson G, et al.

Department of Pharmacology, Jefferson Cancer Institute, Jefferson Medical College, Philadelphia, Pennsylvania 19107, USA.

Recent evidence suggests that mammalian cysteine proteases related to Caenorhabditis elegans CED-3 are key components of mammalian programmed cell death or apoptosis. We have shown recently that the CPP32 and Mch2 alpha cysteine proteases cleave the apoptotic markers poly(ADP-ribose) polymerase (PARP) and lamins, respectively. Here we report the cloning of a new Ced-3/interleukin 1 beta-converting enzyme-related gene, designated Mch3, that encodes a protein with the highest degree of homology to CPP32 compared to other family members. An alternatively spliced isoform, named Mch3 beta, was also identified. Bacterially expressed recombinant Mch3 has intrinsic autocatalytic/autoactivation activity. The specific activity of Mch3 alpha toward the peptide substrate DEVD-7-amino-4-methylcoumarin and PARP resembles that of CPP32. Like interleukin 1 beta-converting enzyme and CPP32, the active Mch3 alpha is made of two subunits derived from a precursor (proMch3 alpha). It was of interest that recombinant CPP32-p17 subunit can form an active heteromeric enzyme complex with recombinant Mch3 alpha-p12 subunit and vice versa, as determined by the ability of the heteromeric complexes to induce apoptosis in Sf9 cells. These data suggest that proMch3 alpha and proCPP32 can interact to form an active Mch3 alpha/CPP32 heteromeric complex. We also provide evidence that CPP32 can efficiently cleave proMch3 alpha, but not the opposite, suggesting that Mch3 alpha activation in vivo may depend in part on CPP32 activity. The high degree of conservation in structure and specific activity and the coexistence of Mch3 alpha and CPP32 in the same cell suggests that the PARP cleavage activity observed during apoptosis cannot solely be attributed to CPP32 but could also be an activity of Mch3 alpha.

PMID: 8521391 [PubMed - indexed for MEDLINE]

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L3 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
1999203526 Document Number: 99203526. PubMed ID: 10103059. Cleavage of transcription factor SP1 by caspases during anti-IgM-induced B-cell apoptosis. Rickers A; Peters N; Badock V; Beyaert R; Vandenabeele P; Dorken B; Bommert K. (Medizinische Onkologie und Tumorimmunologie, Max Delbuck Center for Molecular Medicine, Berlin-Buch, Germany.) EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 Apr) 261 (1) 269-74. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Apoptosis is instrumental in the processes generating the diversity of the B-cell repertoire. Autoreactive B-cells are eliminated by anti-IgM crosslinking after encountering self-antigens, but precise mechanisms leading to B-cell apoptosis are still not well understood. We report here the cleavage of the transcription factor SP1 in the human Burkitt lymphoma cell line BL60 during anti-IgM-induced apoptosis. Western blot analysis revealed two cleavage products of approximately 68 kDa and 45 kDa after

induction of apoptosis. Cleavage could be completely inhibited by zDEVD-fmk, an inhibitor specific for caspase 3-like proteases. In-vitro cleavage of recombinant SP1 by recombinant caspase 3 (CPP32) or caspase 7 (**Mch 3**) results in similar cleavage products as those observed in vivo. Recombinant caspase 6 (Mch 2) primarily generates a 68-kDa cleavage product, as observed after calcium ionophore (CaI) induced B-cell apoptosis. In contrast, caspase 1 (ICE) did not cleave SP1 in vitro. The time course of SP1 cleavage during anti-IgM-induced apoptosis is paralleled by an increase of caspase activity measured by DEVD-p-nitroanilide (DEVD-pNA) cleavage. DNA band-shift assays revealed a decrease in the intensity of the full length SP1/DNA complex and an increase in the intensity of a smaller complex due to the binding of one SP1 cleavage product. By Edman sequencing we could identify a caspase 3 cleavage site after Asp584 (D584AQPQAGR), generating a 22-kDa C-terminal SP1 protein fragment which still contains the DNA binding site. Our results show the cleavage of the human transcription factor SP1 in vivo and in vitro, underlining the central role of caspase 3-like proteases during the process of anti-IgM-induced apoptosis.

L3 ANSWER 2 OF 4 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
1998191033 EMBASE Fas-mediated apoptosis in mouse hepatocytes involves the processing and activation of caspases. Jones R.A.; Johnson V.L.; Buck N.R.; Dobrota M.; Hinton R.H.; Chow S.C.; Kass G.E.N.. Dr. G.E.N. Kass, School of Biological Sciences, University of Surrey, Guildford, Surrey GU2 5XH, United Kingdom. Hepatology 27/6 (1632-1642) 1998.
Refs: 73.
ISSN: 0270-9139. CODEN: HPTLD. Pub. Country: United States. Language: English. Summary Language: English.

AB The mechanism of Fas antigen-induced hepatocyte apoptosis was investigated. Using a monoclonal **antibody** directed against the Fas antigen, apoptosis was induced in freshly isolated murine hepatocytes within 90 minutes of **antibody** addition as assessed by plasma membrane bleb formation, chromatin condensation, and DNA fragmentation. Pretreatment of the cells with the caspase inhibitors, N-acetyl-Asp-Glu-Val-Asp aldehyde (Ac-DEVD-CHO), benzyloxycarbonyl-Val-Ala-DL-Asp-fluoromethylketone (Z-VADFMK), or Z-Asp- 2,6-dichlorobenzoyloxymethylketone inhibited anti-Fas-mediated apoptosis. Likewise, the serine protease inhibitors, N-tosyl-L-phenyl chloromethyl ketone (TPCK) and 3,4-dichloroisocoumarin (DCI), prevented apoptosis, whereas N-tosyl-L-lysine chloromethyl ketone (TLCK), Ac-Leu-Leu-L-norleucinal, Ac- Leu-Leu-L-methional, and trans-epoxysuccinyl-L-leucylamido-(4- guanidino)butane were without effect. Examination of CED-3/caspase-3 related caspases revealed that pro-caspases-3 (CPP32) and -7 (**Mch-3**.alpha.) were rapidly processed after Fas antigen stimulation. Caspase-7 was further cleaved to form the catalytically active subunits. In contrast, the p17 subunit of caspase-3 was not detected, indicating slow formation or rapid degradation. The activation of CED-3-related caspases was further confirmed by an increase in the rate of Z-DEVD-7-amino-4-trifluoromethylcoumarin (Z-DEVD-AFC) hydrolysis that was sensitive to Ac-DEVD-CHO and was inhibited by pretreatment of the cells with TPCK but not by DCI. In contrast, no increase in the rates of hydrolysis of Z-YVAD-AFC, a substrate for caspase-1, was detected. Investigation of the in situ proteolytic cleavage of the CED-3 related caspases substrate, poly(ADP-ribose) polymerase, revealed that this protein was not degraded in hepatocytes undergoing Fas-mediated apoptosis. Taken together, our results show that processing of caspases, in particular, caspases-7 and -3, occurs during Fas-induced apoptosis of mouse hepatocytes and suggest a role of these proteases as well as serine protease(s) in the apoptotic response.

L3 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
1998:507808 Document No.: PREV199800507808. Monoclonal **antibodies** against differentiating mesenchyme cells in larvae of the ascidian

Halocynthia roretzi. Kim, Gil Jung; Nishida, Hiroki (1). (1) Dep. Life Sci., Tokyo Inst. Technol., Nagatsuta, Midori-ku, Tokohama 226-8501 Japan. Zoological Science (Tokyo), (Aug., 1998) Vol. 15, No. 4, pp. 553-559. ISSN: 0289-0003. Language: English.

AB Mechanisms of cell specification of mesenchyme during ascidian embryogenesis are poorly understood. This is because no good molecular markers have been available to evaluate differentiation of the mesenchyme cells. To obtain molecular markers of mesenchyme differentiation, we established monoclonal **antibodies**, Mch-1 and **Mch-3**, that recognize antigens present in the mesenchyme cells of the larva of Halocynthia roretzi. The antigens recognized by both **antibodies** start to be detectable in the mesenchyme cells at the late tailbud stage. The **Mch-3 antibody** specifically recognized all mesenchyme cells of the larva, whereas-the Mch-1 **antibody** stained the cells only in the anterior portions of mesenchyme clusters in the trunk region of the larva. The Mch-1 **antibody** also stained trunk lateral cells. In addition, both **antibodies** recognized the mesenchyme cells in the ventro-lateral boundary between endoderm and epidermis that are migrating to the anterior head region of the larva. The partial embryos that originated from the mesenchymelineage cells at the 8-cell stage expressed the Mch-1 and **Mch-3** antigens. The Mch-11 and **Mch-3** **antibodies** will be useful as immunological probes for studying the specification mechanisms of mesenchyme cells.

L3 ANSWER 4 OF 4 MEDLINE DUPLICATE 4

97341172 Document Number: 97341172. PubMed ID: 9195941. Interferon-gamma modulates a p53-independent apoptotic pathway and apoptosis-related gene expression. Ossina N K; Cannas A; Powers V C; Fitzpatrick P A; Knight J D; Gilbert J R; Shekhtman E M; Tomei L D; Umansky S R; Kiefer M C. (LXR Biotechnology Inc., Richmond, California 94804, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jun 27) 272 (26) 16351-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Interferon (IFN)-gamma increases the sensitivity of tumor cell lines, many of which are p53 mutants, to tumor necrosis factor-alpha-mediated and anti-Fas **antibody**-mediated cell death. To better understand the mechanism of IFN-gamma action in modulating the cell death response independently of p53 function, we analyzed the death of the human colon adenocarcinoma cell line, HT-29, following treatment with IFN-gamma and various cytotoxic agents. Here we show that IFN-gamma modulates cell death by sensitizing the cells to killing by numerous pro-apoptotic stimuli but not pro-necrotic stimuli. Furthermore, we show that select genes from several important apoptosis-related gene families are induced by IFN-gamma, including the apoptosis-signaling receptors CD95 (Fas/APO-1) and TNFR 1 and interleukin-1beta-converting enzyme (Ice) family members Ice, CPP32 (Yama, apopain), ICErel-II (TX, Ich-2), **Mch-3** (ICE-LAP3, CMH-1), Mch-4, and Mch-5 (MACH, FLICE). Of the bcl-2 family members, IFN-gamma directly induced bak but notably not bax, which is activated by p53. The IFN-responsive transcriptional activator interferon regulatory factor-1 was also strongly induced and translocated into the nucleus following IFN-gamma treatment. We propose that IFN-gamma modulates a p53-independent apoptotic pathway by both directly and indirectly inducing select apoptosis-related genes.

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L5 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS

2002:622284 TGF-.beta. latency-associated peptides (LAPs) in human dentin matrix and pulp. Sloan, A. J.; Moseley, R.; Dobie, K.; Waddington, R. J.; Smith, A. J. (Oral Biology, School of Dentistry, University of Birmingham, Birmingham, UK). Connective Tissue Research, 43(2-3), 381-386 (English) 2002. CODEN: CVTRBC. ISSN: 0300-8207. Publisher: Taylor & Francis Ltd..

AB Transforming growth factor (TGF)-.beta.s in dentin matrix provide a pool of bioactive mols., but assocn. with latency-assocd. peptides (LAPs) may influence their activity. The authors investigated TGF-.beta.1, .beta.2, and -.beta.3 LAP expression in sound and carious human teeth. Teeth were fixed and processed immediately following extn. prior to staining with rabbit polyclonal **antibodies** to the TGF-.beta. LAPs. A sol. dentin matrix fraction was prepd. from dissected human dentin and sequential extn. of pulpal ECM was performed prior to purifn. Fractions were Western blotted and probed with the LAP **antibodies**. All three LAPs were present in odontoblasts, cells of the pulp, and predentin; however, no staining of mineralized dentin matrix was seen. Similar patterns of expression were seen in carious tissue. Expression of TGF-.beta. LAPs in cells and pulpal matrix of healthy and carious teeth will be important in regulation of TGF-.beta. activity and may modulate the tissue response to injury.

L5 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS

1997:761953 Document No. 128:31833 Cloning of human interleukin-1.beta. converting enzyme-like apoptotic protease-6 and its diagnostic and therapeutic applications. Dixit, Vishva M.; He, Wei-wu; Ruben, Steven M.; Kikly, Kristine K. (Smithkline Beecham Corp., USA; Human Genome Sciences, Inc.; University of Michigan). Eur. Pat. Appl. EP 808904 A2 19971126, 44 pp. DESIGNATED STATES: R: BE, CH, DE, DK, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 1997-303397 19970519. PRIORITY: US 1996-17949 19960520; US 1996-20344 19960523; US 1996-18961 19960605.

AB Members of the ICE/Ced-3 gene family are likely effector components of the cell death machinery. A novel member of this family designated ICE-LAP-6 is provided. By phylogenetic anal., ICE-LAP6 is classified into the Ced-3 subfamily which includes Ced-3, Yama/CPP32/apopain, Mch2, and ICE-**LAP3**/Mch3/CMH-1. Interestingly, ICE-LAP6 contains an active site QACGG pentapeptide, rather than the QACRG pentapeptide shared by other family members. Overexpression of ICE-LAP6 induces apoptosis in MCF7 breast carcinoma cells. More importantly, ICE-LAP6 is proteolytically processed into an active cysteine protease by granzyme B, an important component of cytotoxic T cell-mediated apoptosis. Once activated, ICE-LAP6 is able to cleave the death substrate poly(ADP-ribose) polymerase into signature apoptopic fragments. Also disclosed are methods for utilizing such ICE LAP-6 for the treatment of a susceptibility to viral infection, tumorogenesis, and to diseases and defects in the control embryogenesis and tissue homeostasis, and the nucleic acid sequences described may be employed in an assay for ascertaining such susceptibility. Agonists and antagonists of ICE LAP-6 may also be used to treat various disease states.

L5 ANSWER 3 OF 4 MEDLINE DUPLICATE 1

97341172 Document Number: 97341172. PubMed ID: 9195941. Interferon-gamma modulates a p53-independent apoptotic pathway and apoptosis-related gene expression. Ossina N K; Cannas A; Powers V C; Fitzpatrick P A; Knight J D; Gilbert J R; Shekhtman E M; Tomei L D; Umansky S R; Kiefer M C. (LXR Biotechnology Inc., Richmond, California 94804, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jun 27) 272 (26) 16351-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Interferon (IFN)-gamma increases the sensitivity of tumor cell lines, many of which are p53 mutants, to tumor necrosis factor-alpha-mediated and anti-Fas **antibody**-mediated cell death. To better understand the

mechanism of IFN-gamma action in modulating the cell death response independently of p53 function, we analyzed the death of the human colon adenocarcinoma cell line, HT-29, following treatment with IFN-gamma and various cytotoxic agents. Here we show that IFN-gamma modulates cell death by sensitizing the cells to killing by numerous pro-apoptotic stimuli but not pro-necrotic stimuli. Furthermore, we show that select genes from several important apoptosis-related gene families are induced by IFN-gamma, including the apoptosis-signaling receptors CD95 (Fas/APO-1) and TNFR 1 and interleukin-1beta-converting enzyme (Ice) family members Ice, CPP32 (Yama, apopain), ICErel-II (TX, Ich-2), Mch-3 (ICE-**LAP3**, CMH-1), Mch-4, and Mch-5 (MACH, FLICE). Of the bcl-2 family members, IFN-gamma directly induced bak but notably not bax, which is activated by p53. The IFN-responsive transcriptional activator interferon regulatory factor-1 was also strongly induced and translocated into the nucleus following IFN-gamma treatment. We propose that IFN-gamma modulates a p53-independent apoptotic pathway by both directly and indirectly inducing select apoptosis-related genes.

L5 ANSWER 4 OF 4 MEDLINE
96214865 Document Number: 96214865. PubMed ID: 8617712. Molecular ordering of the cell death pathway. Bcl-2 and Bcl-xL function upstream of the CED-3-like apoptotic proteases. Chinnaiyan A M; Orth K; O'Rourke K; Duan H; Poirier G G; Dixit V M. (Department of Pathology, University of Michigan Medical School, Ann Arbor 48109, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Mar 1) 271 (9) 4573-6. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Genetic analyses of Caenorhabditis elegans has identified three genes that function in the regulation of nematode cell death. Mammalian homologs of two of these genes, ced-9 and ced-3, have been identified and comprise proteins belonging to the Bcl-2 and ICE families, respectively. To date, it is unclear where the negative regulators, ced-9 and bcl-2, function relative to the death effectors, ced-3 and the mammalian ced-3 homologs, respectively. Here, the molecular order of the cell death pathway is defined. Our results establish that Bcl-2 and Bcl-xL function upstream of two members of the ICE/CED-3 family of cysteine proteases, Yama (CPP32/apopain) and ICE-**LAP3** (Mch3).

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L7 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:4427 Document No.: PREV200200004427. Identity of cutaneous sensory neurons containing VRL-1 in wildtype and VR1-KO mice. Koerber, H. R. (1); Woodbury, C. J. (1); Caterina, M. J.; Koltzenburg, M.. (1) Neurobiology, School of Medicine, University of Pittsburgh, Pittsburgh, PA USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2465. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001 ISSN: 0190-5295. Language: English.

AB Mice lacking VR1 show a reduced heat sensitivity of nociceptors. Here we asked whether the VR1 homologue VRL-1 could be involved in mediating the remaining heat response. Adult mice were anesthetized (ketamine/xylazine) and perfused with chilled oxygenated artificial CSF (aCSF-O2). The spinal cord, 7-9 attached dorsal cutaneous nerves and skin were isolated and placed in a chamber with a circulating bath of aCSF-O2. Sensory neuron somata were impaled, their mechanical and thermal response properties were

determined, and one soma/ganglion injected with Neurobiotin (NB). DRG sections were reacted with antisera for VRL-1 and CGRP, or VR1 and appropriate Cy3 and Cy5-secondary **antibodies**. Stained somata were visualized using avidin-FITC. The somata of 29 identified fibers in 4 VR1-KO (16) and 4 WT (13) mice were recovered. Of 16 C-fibers identified in VR1-KO, 12 were recovered with 8 mechanonociceptors (CM) 2/4 VRL-1+, 0/3 CGRP+, 7 mechano-heat nociceptors (**CMH**) **1**/7 VRL-1+, 1/5 CGRP+ and 1 low mechanical threshold-cooling fiber (CLTM) 1/1 VRL-1+. In addition 3/3 myelinated mechano-nociceptors (HTM) were also found to be VRL-1+. Results in WT mice were similar, CM-0/4 VRL-1+, 0/3 VR1+, 0/1 CGRP+; **CMH** **1**/3 VRL-1+, 0/3 VR1+; CM-cooling, 1/1 VRL-1+, 0/1 VR1+; HTM 1/2 VRL-1+, 1/2 CGRP+. Four fibers innervating hair follicles were also stained in both KO and WT mice with 2/4 being VRL-1+. In conclusion, VRL-1 was most frequently found in the somata of myelinated HTM, but was also seen in some non-nociceptors. Amongst C-fibers heat sensitivity was not correlated with VRL-1 content.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS

1997:397384 Document No. 127:14126 Human cysteine protease **CMH-1** cDNA sequence, recombinant production, gene therapy, and apoptosis inhibitor assay. Su, Michael; Lippke, Judith A. (Vertex Pharmaceuticals Incorporated, USA). PCT Int. Appl. WO 9716552 A1 19970509, 47 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US17431 19961101. PRIORITY: US 1995-7211 19951103; US 1995-7251 19951106; US 1995-558733 19951116.

AB The invention relates to DNA sequences encoding both active and inactive forms of **CMH-1**, a cysteine protease involved in programmed cell death. The invention further relates to the polypeptides encoded by those DNA sequences and **antibodies** to those polypeptides. The invention also relates to recombinant DNA mols. comprising these DNA sequences, as well as hosts transformed with such recombinant DNA mols. The invention further relates to the use of the DNA sequences of this invention in gene therapy for both promoting and inhibiting apoptosis. The DNA sequences of this invention are also useful in diagnosing cells which have the potential to undergo apoptosis. Finally, the polypeptides encoded by the DNA sequences of this invention are useful in identifying inhibitors of apoptosis.

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

1997:761953 Document No. 128:31833 Cloning of human interleukin-1.beta. converting enzyme-like apoptotic protease-6 and its diagnostic and therapeutic applications. Dixit, Vishva M.; He, Wei-wu; Ruben, Steven M.; Kikly, Kristine K. (Smithkline Beecham Corp., USA; Human Genome Sciences, Inc.; University of Michigan). Eur. Pat. Appl. EP 808904 A2 19971126, 44 pp. DESIGNATED STATES: R: BE, CH, DE, DK, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 1997-303397 19970519. PRIORITY: US 1996-17949 19960520; US 1996-20344 19960523; US 1996-18961 19960605.

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L7 ANSWER 4 OF 4 MEDLINE DUPLICATE 1
97341172 Document Number: 97341172. PubMed ID: 9195941. Interferon-gamma modulates a p53-independent apoptotic pathway and apoptosis-related gene expression. Ossina N K; Cannas A; Powers V C; Fitzpatrick P A; Knight J D; Gilbert J R; Shekhtman E M; Tomei L D; Umansky S R; Kiefer M C. (LXR Biotechnology Inc., Richmond, California 94804, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jun 27) 272 (26) 16351-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Interferon (IFN)-gamma increases the sensitivity of tumor cell lines, many of which are p53 mutants, to tumor necrosis factor-alpha-mediated and anti-Fas **antibody**-mediated cell death. To better understand the mechanism of IFN-gamma action in modulating the cell death response independently of p53 function, we analyzed the death of the human colon adenocarcinoma cell line, HT-29, following treatment with IFN-gamma and various cytotoxic agents. Here we show that IFN-gamma modulates cell death by sensitizing the cells to killing by numerous pro-apoptotic stimuli but not pro-necrotic stimuli. Furthermore, we show that select genes from several important apoptosis-related gene families are induced by IFN-gamma, including the apoptosis-signaling receptors CD95 (Fas/APO-1) and TNFR 1 and interleukin-1beta-converting enzyme (Ice) family members Ice, CPP32 (Yama, apopain), ICErel-II (TX, Ich-2), Mch-3 (ICE-LAP3, **CMH-1**), Mch-4, and Mch-5 (MACH, FLICE). Of the bcl-2 family members, IFN-gamma directly induced bak but notably not bax, which is activated by p53. The IFN-responsive transcriptional activator interferon regulatory factor-1 was also strongly induced and translocated into the nucleus following IFN-gamma treatment. We propose that IFN-gamma modulates a p53-independent apoptotic pathway by both directly and indirectly inducing select apoptosis-related genes.

```
=> s l1 and caspase 7
L8          201 L1 AND CASPASE 7

=> s l8 and anti-caspase7
L9            0 L8 AND ANTI-CASPASE7

=> s l8 and anti-caspase 7
L10           4 L8 AND ANTI-CASPASE 7

=> dup remove l10
PROCESSING COMPLETED FOR L10
L11           1 DUP REMOVE L10 (3 DUPLICATES REMOVED)

=> d l11 cbib abs
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L11 ANSWER 1 OF 1 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
2000213174 EMBASE Extended half-life and elevated steady-state level of a single-chain Fv intrabody are critical for specific intracellular retargeting of its antigen, **caspase-7**. Zhu Q.; Zeng C.; Huhalov A.; Yao J.; Turi T.G.; Danley D.; Hynes T.; Cong Y.; DiMattia D.; Kennedy S.; Daumy G.; Schaeffer E.; Marasco W.A.; Huston J.S.. Q. Zhu, IntraImmune Therapies Inc., P.O. Box 15599, Boston, MA 02215-0011, United States. quanzhu@tiac.net. Journal of Immunological Methods 231/1-2 (207-222) 1999.

Refs: 47.
ISSN: 0022-1759. CODEN: JIMMBG.
Publisher Ident.: S 0022-1759(99)00158-1. Pub. Country: Netherlands.
Language: English. Summary Language: English.

AB Two single-chain Fv (sFv) **antibodies** (C8 and H2) specific for Mch3/**caspase-7**, a component in the signaling pathway for induction of apoptosis, were genetically fused to different intracellular targeting signals and analyzed by expression in mammalian cells. Immunofluorescence microscopy confirmed that these **anti-caspase-7** intrabodies were expressed in the cellular compartments dictated by their C-terminal trafficking signals. Cytosolic **caspase-7** was successfully retargeted to different subcellular compartments by specific intrabodies through direct association of antigen with intrabody. Sequestration of **caspase-7** in nuclei had a significant biological impact in that the expression of a nuclear-targeted **anti-caspase-7** intrabody in a stable Jurkat cell line markedly inhibited staurosporine- induced apoptosis. The criteria for choosing an optimal intrabody were also evaluated in this study. A gene dosage titration study demonstrated that the C8 intrabody was more potent in retargeting of **caspase-7** than the H2 intrabody, even though the H2 sFv had a higher affinity for **caspase-7** than the C8. Pulse-chase experiments and western blot analysis revealed that the **anti-caspase-7** C8 sFv intrabodies exhibited a long half-life (> 8 h) and high steady-state levels of protein accumulation, while the H2 intrabodies had a half-life of 2 h and less protein at steady state. These results suggest that the choice of sFv as an intrabody depends critically on the intracellular sFv protein having an extended half-life and elevated steady-state level. Thus, extended half-life must be considered together with sFv **antibody** specificity and affinity when choosing an optimal sFv intrabody for functional studies of cellular proteins. (C) 1999 Elsevier Science B.V.

```
=> s l1 and "CPP32"
L12         913 L1 AND "CPP32"

=> s l12 and anti-CPP32
L13          23 L12 AND ANTI-CPP32

=> dup remove l13
PROCESSING COMPLETED FOR L13
L14            5 DUP REMOVE L13 (18 DUPLICATES REMOVED)

=> d l14 1-5 cbib abs
```

L14 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
2002025501 Document Number: 21377082. PubMed ID: 11484854. Blastocystis hominis: evidence for caspase-3-like activity in cells undergoing programmed cell death. Nasirudeen A M; Singh M; Yap E H; Tan K S. (Department of Microbiology, Faculty of Medicine, National University of Singapore, Singapore.) PARASITOLOGY RESEARCH, (2001 Jul) 87 (7) 559-65. Journal code: 8703571. ISSN: 0932-0113. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB We have shown previously that the human intestinal protozoan, Blastocystis hominis, undergoes apoptosis-like programmed cell death (PCD) when exposed to a cytotoxic monoclonal **antibody** (mAb), 1D5. In the present study, ELISA and immunoblot assays employing chicken **anti-CPP32 antibody** suggest that caspase-3-like antigens exist in B. hominis. Using colorimetric and flow cytometric assays for caspase-3 activity, we also observed an increase in activity between 1 h and 6 h after exposure to mAb 1D5, with greatest activity at 6 h. These findings suggest that caspase-3-like proteases play an important role in

B. hominis undergoing PCD, similar to the phenomenon in higher eukaryotic organisms.

L14 ANSWER 2 OF 5 MEDLINE DUPLICATE 2
2001644541 Document Number: 21554436. PubMed ID: 11697122. Synthesis of ascorbate and urate in the ovary of water buffalo. Spagnuolo M S; Cigliano L; Balestrieri M; Porta A; Abrescia P. (Dipartimento di Fisiologia Generale ed Ambientale, Universita di Napoli Federico II via Mezzocannone 8, 80134 Napoli, Italy.) FREE RADICAL RESEARCH, (2001 Sep) 35 (3) 233-43. Journal code: 9423872. ISSN: 1071-5762. Pub. country: Switzerland. Language: English.

AB Blood flow interruption is associated with oxygen depletion and loss of factors for function and survival in downstream tissues or cells. Hypoxia and absence of gonadotropins trigger apoptosis and atresia in the ovary. We studied the antioxidant response of follicular cells to plasma deprivation in ovaries dissected from water buffalo. Aliquots of follicular fluid were aspirated from each antral follicle, before and during incubation of the ovaries at 39 degrees C. Urate, ascorbate, retinol and alpha-tocopherol in the fluid were, titrated by High Performance Liquid Chromatography (HPLC) with spectrophotometric or spectrofluorimetric detection. The total antioxidant capacity of follicular fluid was determined as absorbance decrease, following addition of a source of radical chromophores. The more the incubation progressed, the higher levels of urate, ascorbate and total antioxidant capacity were found. Conversely, changes in concentration of the liposoluble antioxidants were not observed. Ascorbate synthesizing activity in the follicle was demonstrated by detecting the enzyme L-gulono-gamma-lactone oxidase in microsomes prepared from granulosa cells. These cells were also analyzed for the expression of the enzyme **CPP32**. The enzyme level, measured as DEVD-p-nitroanilide cleaving activity, was found related with the immunoreactivity to **anti-CPP32 antibodies**. Negative correlation between the enzyme activity (which is known to be induced by peroxynitrite) and the follicular level of urate (which scavenges peroxynitrite) was also observed. The amount of nitrotyrosine, a product of peroxynitrite attack on proteins, was measured in follicular fluids by Enzyme Linked ImmunoSorbent Assay (ELISA). This amount was found positively correlated with the **CPP32** activity, and negatively correlated with the urate level in follicular fluid. Alterations in concentrations of ascorbate or urate may be associated with oxidative stress during follicular atresia.

L14 ANSWER 3 OF 5 MEDLINE DUPLICATE 3
2000400174 Document Number: 20383263. PubMed ID: 10928128. Reduced expression of ICE/caspase1 and **CPP32**/caspase3 in human hepatocellular carcinoma. Fujikawa K; Shiraki K; Sugimoto K; Ito T; Yamanaka T; Takase K; Nakano T. (First Department of Internal Medicine, Mie University School of Medicine, Japan.) ANTICANCER RESEARCH, (2000 May-Jun) 20 (3B) 1927-32. Journal code: 8102988. ISSN: 0250-7005. Pub. country: Greece. Language: English.

AB The interleukin-1(-converting enzymes (ICE)/caspase1 and the **CPP32** /caspase3, cysteine proteases, play an important role in the maintenance of homeostasis by inducing apoptosis. Since human hepatocellular carcinomas (HCCs) demonstrate strong resistance to apoptosis, we investigated the expression of ICE and **CPP32** in human HCCs. Reverse transcription PCR analysis revealed that one out of five HCC tissues showed no band of ICE mRNA and two out of five HCC tissues showed no band of **CPP32** mRNA. An immunohistochemical study of 20 cases of HCC tissues and non-tumor parts revealed that immunoreactivity of ICE and **CPP32** was preferentially observed in the cytoplasm, appearing as a diffuse and homogeneous pattern. Some nuclei also stained with anti-ICE **antibody** or **anti-CPP32 antibody** and demonstrated apoptotic features. Overall, the expression of ICE and **CPP32** were significantly down-regulated in

the HCCs compared to nontumor cells. In situ nick end labeling method (TUNEL) labeling index significantly decreased according to the decreasing staining intensity of **CPP32**. However, there was no tendency for the TUNEL labeling index to decrease with decreasing ICE staining intensity. Our results suggested that the expression of ICE and **CPP32** were down-regulated and that especially reduced expression of **CPP32** may contribute to resistance against apoptosis in human HCCs.

L14 ANSWER 4 OF 5 MEDLINE DUPLICATE 4

97309310 Document Number: 97309310. PubMed ID: 9166725. Characterization of **CPP32**-like protease activity following apoptotic challenge in SH-SY5Y neuroblastoma cells. Posmantur R; McGinnis K; Nadimpalli R; Gilbertsen R B; Wang K K. (Department of Immunopathology, Parke-Davis Pharmaceutical Research, Warner-Lambert Company, Ann Arbor, Michigan 48105, U.S.A.) JOURNAL OF NEUROCHEMISTRY, (1997 Jun) 68 (6) 2328-37. Journal code: 2985190R. ISSN: 0022-3042. Pub. country: United States. Language: English.

AB We characterized the activation of interleukin-1beta-converting enzyme (ICE)-like proteases (caspases) in human neuroblastoma cells (SH-SY5Y) following challenge with staurosporine, an established agent known to induce apoptosis. Time course analyses of lactate dehydrogenase release detected a significant increase in cell death as early as 6 h that continued at least until 24 h following staurosporine treatment. Western blot analyses using anti-poly(ADP-ribose) polymerase (anti-PARP) and **anti-CPP32 antibodies** revealed proteolytic processing of **CPP32** (an ICE homologue) as well as fragmentation of PARP as early as 3 h following staurosporine challenge. Furthermore, the hydrolysis of the **CPP32** substrate acetyl-DEVD-7-amido-4-methylcoumarin was detected as early as 3 h and became maximal at 6 h after staurosporine challenge, suggesting a delayed and sustained period of **CPP32**-like activation. In addition, we used the first immunohistochemical examination of **CPP32** and PARP in cells following an apoptotic challenge. The localization of **CPP32** in untreated SH-SY5Y cells was exclusively restricted to the cytoplasm. Following staurosporine challenge there was a condensing of **CPP32** immunofluorescence from the cytoplasm to a region adjacent to the plasma membrane. In contrast, PARP immunofluorescence was evenly distributed in the nucleus in untreated SH-SY5Y cells and on staurosporine challenge was found to be associated with condensed chromatin. It is important that a pan ICE inhibitor [carbobenzoxy-Asp-CH2OC(O)-2,6-dichlorobenzene] was able to attenuate lactate dehydrogenase release and PARP and **CPP32** cleavage and altered immunohistochemical staining patterns for PARP and **CPP32** following staurosporine challenge.

L14 ANSWER 5 OF 5 MEDLINE DUPLICATE 5

1998007465 Document Number: 98007465. PubMed ID: 8987778. Activation of the CED3/ICE-related protease **CPP32** in cerebellar granule neurons undergoing apoptosis but not necrosis. Armstrong R C; Aja T J; Hoang K D; Gaur S; Bai X; Alnemri E S; Litwack G; Karanewsky D S; Fritz L C; Tomaselli K J. (IDUN Pharmaceuticals, Inc., La Jolla, California 92037, USA.) JOURNAL OF NEUROSCIENCE, (1997 Jan 15) 17 (2) 553-62. Journal code: 8102140. ISSN: 0270-6474. Pub. country: United States. Language: English.

AB Neuronal apoptosis occurs during nervous system development and after pathological insults to the adult nervous system. Inhibition of CED3/ICE-related proteases has been shown to inhibit neuronal apoptosis in vitro and in vivo, indicating a role for these cysteine proteases in neuronal apoptosis. We have studied the activation of the CED3/ICE-related protease **CPP32** in two in vitro models of mouse cerebellar granule neuronal cell death: K+/serum deprivation-induced apoptosis and glutamate-induced necrosis. Pretreatment of granule neurons with a selective, irreversible inhibitor of CED3/ICE family proteases,

ZVAD-fluoromethylketone, specifically inhibited granule neuron apoptosis but not necrosis, indicating a selective role for CED3/ICE proteases in granule neuron apoptosis. Extracts prepared from apoptotic, but not necrotic, granule neurons contained a protease activity that cleaved the **CPP32** substrate Ac-DEVD-aminomethylcoumarin. Induction of the protease activity was prevented by inhibitors of RNA or protein synthesis or by the CED3/ICE protease inhibitor. Affinity labeling of the protease activity with an irreversible CED3/ICE protease inhibitor, ZVK(biotin)D-fluoromethylketone, identified two putative protease subunits, p20 and p18, that were present in apoptotic but not necrotic granule neuron extracts. Western blotting with **antibodies** to the C terminus of the large subunit of mouse **CPP32** (**anti-CPP32**) identified p20 and p18 as processed subunits of the **CPP32** proenzyme. **Anti-CPP32** specifically inhibited the DEVD-amc cleaving activity, verifying the presence of active **CPP32** protease in the apoptotic granule neuron extracts. Western blotting demonstrated that the **CPP32** proenzyme was expressed in granule neurons before induction of apoptosis. These results demonstrate that the CED3/ICE homolog **CPP32** is processed and activated during cerebellar granule neuron apoptosis. **CPP32** activation requires macromolecular synthesis and CED3/ICE protease activity. The lack of **CPP32** activation during granule neuron necrosis suggests that proteolytic processing and activation of CED3/ICE proteases are specific biochemical markers of apoptosis.

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=> s l1 and Yama
L15         101 L1 AND YAMA

=> s l15 and anti-yama
L16           0 L15 AND ANTI-YAMA

=> s l15 and caspase 3
L17          42 L15 AND CASPASE 3

=> s l17 and anti-caspase 3
L18           0 L17 AND ANTI-CASPASE 3

=> dup remove l17
PROCESSING COMPLETED FOR L17
L19          12 DUP REMOVE L17 (30 DUPLICATES REMOVED)

=> d l19 1-12 cbib abs

L19  ANSWER 1 OF 12     MEDLINE                          DUPLICATE 1
2001119269  Document Number: 21066533.    PubMed ID: 11146406.   Transition of
     apoptotic resistant vascular smooth muscle cells to troptotic sensitive
     state is correlated with downregulation of c-FLIP. Imanishi T; Hano T;
     Nishio I; Liles W C; Schwartz S M; Han D K. (Division of Cardiology,
     Department of Medicine, Wakayama Medical College, Wakayama City, Japan..
     imanashi@wakayama.hosp.gobo.jp) . JOURNAL OF VASCULAR RESEARCH, (2000
     Nov-Dec) 37 (6) 523-31.  Journal code: 9206092. ISSN: 1018-1172. Pub.
     country: Switzerland. Language: English.
AB   Fas and its ligand, FasL, are a receptor-ligand pair identified as
     promoting cell death in several tissues. Vascular smooth muscle cells
     (VSMCs) are resistant to FasL or anti-Fas antibody (Ab) signal,
     and a number of in vitro studies show that VSMC death can only be induced
     by anti-Fas Ab or FasL in the presence of protein inhibitor or additional
     inflammatory mediators. It remains to be clarified whether known,
     constitutively expressed cytoprotective molecules are reduced by protein
     inhibitor, thereby accounting for sensitization to cell death by Fas/FasL
     signaling. We found that Fas mRNA and protein exist in several primary
     VSMCs, as previously reported. We also demonstrated (1) that critical
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death-signaling molecules, such as FADD, caspase-1/ICE, and **caspase-3/YAMA**, are present in these VSMCs, (2) that human VSMCs contain high concentrations of c-FLIP (3) and that following treatment with the protein inhibitor, CHX, cell extracts showed a decrease in c-FLIP protein that was dose- and time-dependent on the degree of apoptosis and inversely correlated with both caspase-8 and -3 activity. In contrast, there was neither a change nor an even modest upregulation of Bcl-2 family, even after 12 h of treatment with CHX. Taken together, these results may provide a novel insight into atherogenesis and suggest that c-FLIP may contribute to an apoptosis-resistant state of VSMC, and that a downregulation of c-FLIP may render VSMCs susceptible to apoptosis.

L19 ANSWER 2 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)
2000:392523 The Genuine Article (R) Number: 315XQ. Lactacystin activates FLICE (caspase 8) protease and induces apoptosis in Fas-resistant adult T-cell leukemia cell lines. Yamada Y (Reprint); Sugahara K; Tsuruda K; Nohda K; Mori N; Hata T; Maeda T; Hayashibara T; Joh T; Honda M; Tawara M; Tomonaga M; Miyazaki Y; Kamihira S. NAGASAKI UNIV, SCH MED, DEPT LAB MED, 1-7-1 SAKAMOTO, NAGASAKI 8528501, JAPAN (Reprint); NAGASAKI UNIV, DEPT PREVENT MED & AIDS RES, RES FIELD PATHOGENESIS & CLIN SCI, NAGASAKI 852, JAPAN; NAGASAKI UNIV, SCH MED, DEPT HEMATOL, NAGASAKI 852, JAPAN. EUROPEAN JOURNAL OF HAEMATOLOGY (MAY 2000) Vol. 64, No. 5, pp. 315-322. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0902-4441. Pub. country: JAPAN. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Lactacystin (LC) is a specific inhibitor of the proteasome, and has recently been shown to induce apoptosis in certain cell lines. In the present study, we established Fas-resistant adult T-cell leukemia (ATL) cell subclones RSO4 and RST1 from their parental Fas-sensitive cell lines SO4 and ST1, and examined whether LC can overcome Fas resistance. LC completely inhibited proteasome function as determined by a peptidyl-MCA substrate (LLVY-MCA and LLE-MCA), and induced apoptosis in these cell lines irrespective of Fas sensitivity at low concentrations (similar to 10 mu M). LC induced the activation of **caspase 3** (CPP32/**Yama**) and caspase 6 proteases in an identical manner to Fas-mediated apoptosis. Moreover, LC induced the activation of caspase 8 (FLICE) protease, which is the initiator of the Fas-mediated apoptotic cascade. Synthesized proteasome inhibitory peptide MG-115 (ZLLnV-CHO) also induced apoptosis in these cell lines; These results indicated that proteasome inhibitors overcome Fas-resistance by bypassing the proximal part of the Fas signal. Inhibition of the proteasome function may be a new strategy for the treatment of ATL.

L19 ANSWER 3 OF 12 MEDLINE DUPLICATE 2
1999313557 Document Number: 99313557. PubMed ID: 10386985. Activation of **caspase-3** in developmental models of programmed cell death in neurons of the substantia nigra. Jeon B S; Kholodilov N G; Oo T F; Kim S Y; Tomaselli K J; Srinivasan A; Stefanis L; Burke R E. (Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York 10032, USA.) JOURNAL OF NEUROCHEMISTRY, (1999 Jul) 73 (1) 322-33. Journal code: 2985190R. ISSN: 0022-3042. Pub. country: United States. Language: English.
AB Programmed cell death has been proposed to play a role in the death of neurons in acute and chronic degenerative neurologic disease. There is now evidence that the caspases, a family of cysteine proteases, mediate programmed cell death in various cells. In neurons, **caspase-3** (CPP32/**Yama**/apopain), in particular, has been proposed to play a role. We examined the expression of **caspase-3** in three models of programmed cell death affecting neurons of the substantia nigra in the rat: natural developmental neuron death and induced developmental death following either striatal target injury with

quinolinic acid or dopamine terminal lesion with intrastriatal injection of 6-hydroxydopamine. Using an **antibody** to the large (p17) subunit of activated **caspase-3**, we have found that activated enzyme is expressed in apoptotic profiles in all models. Increased p17 immunostaining correlated with increased enzyme activity. The subcellular distribution of activated **caspase-3** differed among the models: In natural cell death and the target injury model, it was strictly nuclear, whereas in the toxin model, it was also cytoplasmic. We conclude that p17 immunostaining is a useful marker for programmed cell death in neurons of the substantia nigra.

L19 ANSWER 4 OF 12 MEDLINE DUPLICATE 3

1999047701 Document Number: 99047701. PubMed ID: 9830064. TRAIL/Apo2L activates c-Jun NH2-terminal kinase (JNK) via caspase-dependent and caspase-independent pathways. Muhlenbeck F; Haas E; Schwenzer R; Schubert G; Grell M; Smith C; Scheurich P; Wajant H. (Institute of Cell Biology and Immunology, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Dec 4) 273 (49) 33091-8. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB In this study we show that TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), also called Apo2L, activates the c-Jun N-terminal kinase (JNK). Interestingly, TRAIL-induced JNK activation occurs in a cell type-specific manner. In HeLa cells, TRAIL-induced JNK activation can be completely blocked with the cysteine protease inhibitor zVAD-fmk, whereas the same inhibitor has no, or even a stimulatory, effect on JNK activation in Kym-1 cells. Hence, TRAIL can engage at least two independent pathways leading to JNK activation, one that is cysteine protease-dependent and one that is cysteine protease-independent. To investigate whether the cysteine protease-dependent signaling of TRAIL leading to JNK activation is related to the apoptotic pathway engaged by this ligand, we investigated HeLa cells stably overexpressing a dominant negative mutant of FADD (Fas-associating protein with death domain) (GFP(green fluorescent protein)DeltaFADD). In these cells, TRAIL-induced cell death and activation of the apoptosis executioner caspase-8 (FLICE/MACH) and **caspase-3** (**YAMA**, CPP-32, Apopain), that belong to caspase subfamily of cysteine proteases, were abrogated, whereas JNK activation remained unaffected and was still sensitive toward z-VAD-fmk. Similar data were found in HeLa cells overexpressing Apo1/Fas and GFPDeltaFADD upon stimulation with agonistic **antibodies**. These data suggest that cross-linking of the TRAIL receptors and Apo1/Fas, respectively, engages a FADD-dependent pathway leading to the activation of apoptotic caspases and, in parallel, a FADD-independent pathway leading to the stimulation of one or more cysteine proteases capable to activate JNK but not sufficient for the induction of cell death.

L19 ANSWER 5 OF 12 MEDLINE

1998430705 Document Number: 98430705. PubMed ID: 9759905. Therapeutic preparations of normal polyspecific IgG (IVIg) induce apoptosis in human lymphocytes and monocytes: a novel mechanism of action of IVIg involving the Fas apoptotic pathway. Prasad N K; Papoff G; Zeuner A; Bonnin E; Kazatchkine M D; Ruberti G; Kaveri S V. (Institut National de la Sante et de la Recherche Medicale U430, Universite Pierre et Marie Curie, Paris, France.) JOURNAL OF IMMUNOLOGY, (1998 Oct 1) 161 (7) 3781-90. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Therapeutic preparations of normal human IgG for i.v. use (i.v.Ig) exhibit a broad spectrum of immunoregulatory activities in vitro and in vivo. I.v.Ig has been shown to inhibit the proliferation of activated B and T lymphocytes and of several autonomously growing cell lines. In this study, we demonstrate that i.v.Ig induces apoptosis in leukemic cells of lymphocyte and monocyte lineage and in CD40-activated normal tonsillar B

cells, involving, at least in part, Fas (CD95/APO-1) and activation of caspases. I.v.Ig-induced apoptosis was higher in Fas-sensitive HuT78 cells than in Fas-resistant HuT78.B1 mutant cells, and soluble Fas inhibited IVIg-induced apoptosis. I.v.Ig immunoprecipitated Fas from Fas-expressing transfectants and recognized purified Fas/glutathione-S-transferase fusion proteins upon immunoblotting. Affinity-purified anti-Fas Abs from i.v.Ig induced apoptosis of CEM T cells at a 120-fold lower concentration than unfractionated i.v.Ig. Inhibitors of cysteine proteases of the caspase family, caspase 1 (IL-1beta-converting enzyme) and **caspase 3** (**Yama**/CPP32b), partially inhibited i.v.Ig-induced apoptosis of CEM cells. Furthermore, cleavage of poly(A)DP-ribose polymerase into an 85-kDa signature death fragment was observed in CEM cells following i.v.Ig treatment. Thus, normal IgG induces apoptosis in lymphocytes and monocytes. Our results provide evidence for a role of Fas, bring new insights into the mechanisms of action of i.v.Ig in autoimmune diseases, and suggest a role of normal Ig in controlling cell death and proliferation.

L19 ANSWER 6 OF 12 SCISEARCH COPYRIGHT 2002 ISI (R)

1998:275870 The Genuine Article (R) Number: ZE957. Synthetic activation of caspases: Artificial death switches. MacCorkle R A; Freeman K W; Spencer D M (Reprint). BAYLOR COLL MED, DEPT MICROBIOL & IMMUNOL, 1 BAYLOR PLAZA, M929, HOUSTON, TX 77030 (Reprint); BAYLOR COLL MED, DEPT MICROBIOL & IMMUNOL, HOUSTON, TX 77030. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (31 MAR 1998) Vol. 95, No. 7, pp. 3655-3660. Publisher: NATL ACAD SCIENCES. 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418. ISSN: 0027-8424. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The development of safe vectors for gene therapy requires fail-safe mechanisms to terminate therapy or remove genetically altered cells. The ideal ''suicide switch'' would be nonimmunogenic and nontoxic when uninduced and able to trigger cell death independent of tissue type or cell cycle stage, By using chemically induced dimerization, we have developed powerful death switches based on the cysteine proteases, caspase-1 ICE (interleukin-1 beta converting enzyme) and **caspase -3 YAMA**, In both cases, aggregation of the target protein is achieved by a nontoxic lipid-permeable dimeric FK506 analog that binds to the attached FK506-binding proteins, FKBPs. We find that intracellular cross-linking of caspase-1 or **caspase-3** is sufficient to trigger rapid apoptosis in a Bcl-x(L)-independent manner, suggesting that these conditional proapoptotic molecules can bypass intracellular checkpoint genes, such as Bcl-x(L), that limit apoptosis. Because these chimeric molecules are derived from autologous proteins, they should be nonimmunogenic and thus ideal for long-lived gene therapy vectors. These properties should also make chemically induced apoptosis useful for developmental studies, for treating hyperproliferative disorders, and for developing animal models to a wide variety of diseases.

L19 ANSWER 7 OF 12 MEDLINE DUPLICATE 4

97382291 Document Number: 97382291. PubMed ID: 9235961. The large subunit of the DNA replication complex C (DSEB/RF-C140) cleaved and inactivated by **caspase-3** (CPP32/**YAMA**) during Fas-induced apoptosis. Ubeda M; Habener J F. (Laboratory of Molecular Endocrinology, Massachusetts General Hospital, Howard Hughes Medical Institute, and Harvard Medical School, Boston, Massachusetts 02114, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Aug 1) 272 (31) 19562-8. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB We report the identification of the large subunit of the DNA replication factor, DSEB/RF-C140, as a new substrate for **caspase-3** (CPP32/**YAMA**), or a very closely related protease activated during Fas-induced apoptosis in Jurkat T cells. DSEB/RF-C140 is a multifunctional DNA-binding protein with sequence homology to

poly(ADP-ribose) polymerase (PARP). This similarity includes a consensus DEVD/G cleavage site for **caspase-3**. Cleavage of DSEB/RF-C140 is predicted to occurs between Asp706 and Gly707, generating 87-kDa and 53-kDa fragments. An antiserum raised against the amino-terminal domain of DSEB/RF-C140 detects a new 87-kDa protein in Jurkat T cells in which apoptosis is activated by a monoclonal **antibody** to Fas. This cleavage occurs shortly after PARP cleavage. In vitro translated DSEB/RF-C140 is specifically cleaved into the predicted fragments when incubated with a cytoplasmic extract from Fas **antibody**-treated cells. Proteolytic cleavage was prevented by substituting Asp706 by an alanine in the DEVD706/G **caspase-3** cleavage site. The cleavage of DSEB/RF-C140 is prevented by iodoacetamide and the specific **caspase-3** inhibitor, tetrapeptide aldehyde Ac-DEVD-CHO, but not by the specific ICE (interleukin-1-converting enzyme) inhibitors: CrmA and Ac-YVAD-CHO, indicating that the protease responsible for the cleavage of DSEB/RF-C140 during Fas-induced apoptosis in Jurkat cells is **caspase-3**, or a closely related protease. This conclusion is reinforced by the fact that recombinant **caspase-3** but not caspase-1 reproduced the "in vivo" cleavage. Inasmuch as the cleavage of DSEB/RF-C140 separates its DNA binding from its association domain, required for replication complex formation, we propose that such a cleavage will impair DNA replication. Recent in vitro mutagenesis support this proposal (Uhlmann, F., Cai, J., Gibbs, E., O'Donnel, M., and Hurwitz, J. (1997) J. Biol. Chem. 272, 10058-10064).

L19 ANSWER 8 OF 12 MEDLINE DUPLICATE 5

97207256 Document Number: 97207256. PubMed ID: 9054391. Selective activation of caspases during apoptotic induction in HL-60 cells. Effects Of a tetrapeptide inhibitor. Polverino A J; Patterson S D. (Amgen Inc., Thousand Oaks, California 91320-1789, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Mar 14) 272 (11) 7013-21. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Apoptosis is a highly regulated biochemical process that results in the selective death of cells. Members of the caspase family of cysteine proteases play a pivotal role in the effector phase of apoptosis. We show that, in HL-60 cells, the addition of either anisomycin, a protein synthesis inhibitor, or geranylgeraniol, an intermediate in the cholesterol biosynthetic pathway, results in a rapid and en masse induction of apoptosis. The levels of actin, p42 and p44 MAPK, JNK1, JNK2, p38, and PCNA were not substantially altered during this process. Although these treatments appear to function by diverse pathways, they both result in the processing and activation of **caspase-3** (CPP32beta/**Yama**/Apopain). In contrast, no activation of caspase-1 (interleukin-1beta converting enzyme (ICE)) was observed. Furthermore, we obtained ambiguous results regarding the activation of caspase-2 (Ich-1) depending on the **antibody** used. Pretreatment of the cells with benzyloxycarbonyl-Val-Ala-Asp-(OMe)-fluoromethylketone (zVAD.fmk), a tetrapeptide inhibitor of caspases, prevented the induction of apoptosis for 24 h. Even after 72 h of treatment, some cells were still alive and progressing through the cell cycle, suggesting that blockage of caspase activity is able to protect cells. These results suggest that selective activation of some caspases is necessary to induce apoptosis in HL-60 cells.

L19 ANSWER 9 OF 12 MEDLINE DUPLICATE 6

1998065786 Document Number: 98065786. PubMed ID: 9403528. Dysregulated expression of neutrophil apoptosis in the systemic inflammatory response syndrome. Jimenez M F; Watson R W; Parodo J; Evans D; Foster D; Steinberg M; Rotstein O D; Marshall J C. (Department of Surgery, University of Toronto, Toronto Hospital, Ontario, Canada.) ARCHIVES OF SURGERY, (1997 Dec) 132 (12) 1263-9; discussion 1269-70. Journal code: 9716528. ISSN: 0004-0010. Pub. country: United States. Language: English.

AB OBJECTIVE: To study the effect of the systemic inflammatory response syndrome (SIRS) or major elective surgery on the apoptosis of circulating polymorphonuclear neutrophils because an activated inflammatory response is terminated, in part, through the programmed cell death, or apoptosis, of its effector cells. DESIGN: A prospective inception cohort study. SETTING: A mixed surgical and medical intensive care unit of an adult tertiary care hospital. PATIENTS: Sixteen patients with SIRS, 7 uninfected patients who had undergone elective aortic aneurysmectomy, and 8 healthy laboratory control subjects. INTERVENTIONS: Serial blood samples were drawn for evaluation of neutrophil apoptosis, activational state, and surface receptor expression by flow cytometry. MAIN OUTCOME MEASURES: Spontaneous apoptosis was significantly delayed in neutrophils from patients with SIRS (8.6%+/-6.8%) and patients who had undergone elective aortic aneurysmectomy (11.0%+/-5.0%) when compared with controls (34.9%+/-6.8%). These neutrophils were activated as evidenced by enhanced respiratory burst activity and augmented surface expression of CD11b. Apoptosis in response to engagement of cell surface Fas (also known as CD95 or APO-1) with an agonistic **antibody** was blunted. Plasma from patients with SIRS or patients who had undergone elective aortic aneurysmectomy suppressed the apoptotic responses of control neutrophils (plasma from patients with SIRS, 18.8%+/-10.3%; plasma from patients who had undergone elective aortic aneurysmectomy, 20.0%+/-6.1%; P<.01). Western blot analysis showed normal expression of the key proapoptotic proteases, interleukin 1beta converting enzyme and CPP32 (also known as **YAMA**, apopain, and **caspase 3**), indicating that delayed apoptosis was not a consequence of decreased levels of proapoptotic enzymes. CONCLUSIONS: Circulating neutrophils from patients with SIRS or from patients who have undergone major elective surgery show delayed expression of constitutive programmed cell death, and antiapoptotic factors are present in the general circulation. While prolonged neutrophil survival may represent an appropriate adaptive response to injury, the presence of activated and apoptosis-resistant cells in an antiapoptotic environment may contribute to the systemic inflammatory injury characteristic of SIRS and predispose to the development of the multiple organ dysfunction syndrome.

≤ LAP-4

L19 ANSWER 10 OF 12 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

97368496 EMBASE Document No.: 1997368496. Induction of apoptosis by cryptophycin 1, a new antimicrotubule agent. Mooberry S.L.; Busquets L.; Tien G.. S.L. Mooberry, Cancer Research Center of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813, United States. sue@crch.hawaii.edu. International Journal of Cancer 73/3 (440-448) 1997.
Refs: 26.
ISSN: 0020-7136. CODEN: IJCNAW. Pub. Country: United States. Language: English. Summary Language: English.

AB The ability of cryptophycin I, a new potent cytotoxic antimicrotubule agent, to initiate apoptosis was studied. Treatment of cells with cryptophycin I (50 pM) rapidly caused morphological changes consistent with the induction of apoptosis. DNA strand breakage and fragmentation of the DNA into oligonucleosome-sized fragments was observed, and this coincided with the loss of cellular DNA. Activation of the cysteine protease CPP32 (**caspase 3**, **YAMA**, apopain), a member of the ICE/CED-3-like protease family of apoptosis effectors, was consistent with the execution of cell death by a coordinated sequence of events. Low concentrations of cryptophycin I caused mitotic arrest with the formation of abnormal mitotic spindles without affecting interphase microtubule structures. Unlike other microtubule active agents, cryptophycin-induced mitotic arrest persisted for only a brief period before the onset of apoptosis. There was no evidence of release from G2/M cell cycle arrest. Our results show that low concentrations of cryptophycin I (50 pM) initiated cell death consistent with apoptosis. These data suggest that the cytotoxic effects of cryptophycin I are due in part to its ability to initiate apoptosis rapidly.

L19 ANSWER 11 OF 12 MEDLINE DUPLICATE 7
97376992 Document Number: 97376992. PubMed ID: 9233763. Involvement of caspase-4(-like) protease in Fas-mediated apoptotic pathway. Kamada S; Washida M; Hasegawa J; Kusano H; Funahashi Y; Tsujimoto Y. (Department of Medical Genetics, Biomedical Research Center, Osaka University Medical School, Suita, Japan.) ONCOGENE, (1997 Jul 17) 15 (3) 285-90. Journal code: 8711562. ISSN: 0950-9232. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Proteases of the caspase family, especially caspase-1 (ICE)(-like), **caspase-3** (CPP32/**Yama**/apopain)(-like) and caspase-8 (MACH/FLICE/Mch5) proteases, are implicated in Fas (APO-1/CD95)-mediated apoptosis. Here, we show that the caspase-4 (TX/ICH-2/ICE(rel)II)(-like) protease, another member of the caspase family, is also involved in Fas-mediated apoptosis, based upon the observations: (i) caspase-4 is processed in response to an agonistic anti-Fas **antibody** treatment, (ii) overexpression of a mutant caspase-4 with active site mutations in both p20 and p10 subunits delays Fas-mediated apoptosis, (iii) microinjected anti-caspase-4 **antibodies** inhibit Fas-mediated apoptosis. Together with our observations that the mutant caspase-4 inhibits the Fas-mediated activation of **caspase-3**(-like) proteases and purified caspase-4 cleaves pro-**caspase-3** to generate a subunit of active form, these results suggest that Fas-mediated apoptosis is driven by a caspase cascade in which the caspase-4(-like) protease transmits a death signal from caspase-8 to **caspase-3** (-like) proteases probably through directly cleaving pro-**caspase -3**(-like) proteases.

L19 ANSWER 12 OF 12 MEDLINE DUPLICATE 8
1998072472 Document Number: 98072472. PubMed ID: 9409814. Differential activity of bcl-2 and ICE enzyme family protease inhibitors on Fas and puromycin-induced apoptosis of glioma cells. Schlapbach R; Fontana A. (University Hospital Zurich, Section of Clinical Immunology, Switzerland.) BIOCHIMICA ET BIOPHYSICA ACTA, (1997 Nov 27) 1359 (2) 174-80. Journal code: 0217513. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB Fas ligand is a potent inducer of apoptosis in human glioma cells by the Fas/Fas ligand pathway. With comparable efficiency, metalloprotease inhibitors including puromycin and bestatin induce apoptosis in glioma cells. To evaluate the involvement of potential components involved in Fas ligand- and metalloprotease inhibitor-induced apoptosis, we investigated the effect of anti human Fas **antibody**, soluble Fas ligand and puromycin on cultures of human malignant glioma cell lines (LN-18, LN-229, T98G). Stimulation with Fas ligand lead to apoptotic cell death within 16 h. Costimulation with the translational inhibitor cycloheximide and the transcription blocker actinomycin D did not reduce Fas ligand toxicity. In contrast, apoptosis induced by puromycin was blocked by cycloheximide and decreased by subtoxic doses of actinomycin D in all three gliomas. Whereas inhibition of caspase activity with the general inhibitor zVAD-fmk resulted in a complete block of Fas ligand-induced cell death, puromycin-mediated apoptosis was found to be unaffected by zVAD-fmk as well as by more specific inhibitors for caspase-1 (Interleukin-1 beta converting enzyme) and **caspase-3** (CPP32/**Yama**). Other prominent components involved in many apoptotic pathways as bcl-2 and reactive oxygen intermediates were also examined. Bcl-2 which protects glioma cells from Fas ligand-induced cell death, was shown to have only a small protective effect on puromycin-induced apoptosis. The tested radical scavengers did not reduce Fas- or puromycin-mediated killing of human glioma cells.

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L20 2 L1 AND "LAP4"

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L21 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
2000:725757 Document No. 133:277843 Protein-protein complexes from Saccharomyces and human and their use in drug and fungicide screening. Giot, Loic; Mansfield, Traci A. (Curagen Corp., USA). PCT Int. Appl. WO 2000060066 A1 20001012, 103 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US8399 20000330. PRIORITY: US 1999-PV127352 19990401.
AB The invention provides complexes of at least two proteins from the yeast S. cerevisiae and from humans and methods of using the same. Purified complexes of two proteins are provided, including chimeric complexes, and chimeric polypeptides and complexes thereof are also provided, as are nucleic acids encoding chimeric polypeptides and vectors and cells contg. the same. Also provided are methods of identifying agents that disrupt polypeptide complexes, methods of identifying complex or polypeptide in a sample, and for removing the same, methods of detg. altered expression of a polypeptide in a subject and methods of treating/preventing disorders involving altered levels of complex or polypeptide. Thus, using a two-hybrid screen, 692 interacting protein pairs were identified in S. cerevisiae. Specific complexes which may be useful for identifying antifungal agents are specifically mentioned. These include microtubules and microtubule-assocd. proteins, coproporphyrinogen III oxidase and gene SED1 cell surface glycoprotein, cell wall-related proteins. Also disclosed are complexes of human proteins, some of which are human orthologs of the Saccharomyces proteins.

L21 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS
1991:56926 Document No. 114:56926 Characterization of and cloning of genes for substrate-specific aminopeptidases of Saccharomyces cerevisiae. Smith, John A.; Chang, Yie Hwa (General Hospital Corp., USA). Eur. Pat. Appl. EP 359164 A2 19900321, 34 pp. DESIGNATED STATES: R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1989-116734 19890909. PRIORITY: US 1988-243733 19880913; US 1988-284244 19881214.
AB Substrate-specific aminopeptidases AP1, AP2, and APX from S. cerevisiae recognizing a limited no. of amino-terminal dipeptides contg. a penultimate isoleucine or a terminal methionine are identified and partially characterized and the gene for AP1 cloned and sequenced. The signal sequence for AP1 that directs the protein to the vacuole is identified and polyclonal **antibodies** raised against this enzyme.

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L22 56 "LAP-3"

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L23 9 L22 AND "LAP-4"

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L24 5 DUP REMOVE L23 (4 DUPLICATES REMOVED)

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L24 ANSWER 1 OF 5 SCISEARCH COPYRIGHT 2002 ISI (R)
1998:807797 The Genuine Article (R) Number: 129FT. Size-dependent, spatial and temporal genetic variation at a leucine aminopeptidase (LAP) locus among blue mussel (Mytilus galloprovincialis) populations along a salinity gradient. Gardner J P A (Reprint); Palmer N L. VICTORIA UNIV WELLINGTON, SCH BIOL SCI, ISL BAY MARINE LAB, POB 600, WELLINGTON, NEW ZEALAND (Reprint). MARINE BIOLOGY (SEP 1998) Vol. 132, No. 2, pp. 275-281. Publisher: SPRINGER VERLAG. 175 FIFTH AVE, NEW YORK, NY 10010. ISSN: 0025-3162. Pub. country: NEW ZEALAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Biochemical genetic variation at a leucine aminopeptidase (LAP) locus is related to salinity variation in several marine bivalve molluscs. This paper details an investigation of the Long Island Sound model of LAP selection (LAP genotype-dependent mortality occurring among newly settled Mytilus edulis mussels) carried out in 1997 among three M. galloprovincialis mussel populations along the salinity gradient of Wellington Harbour, New Zealand. Significant LAP genotypic heterogeneity was observed at the LAP locus between small (<25 mm shell length) and large (> 25 mm shell length) M. galloprovincialis from Petone and Eastbourne (the two sites experiencing the greatest salinity variation), whereas genotypic heterogeneity was not significantly different between small and large mussels from Seatoun (the site experiencing the least salinity variation). The **Lap**(**3**) allele decreased in frequency and the **Lap**(**4**) allele increased in frequency at Petone and Eastbourne, whereas the **Lap**(**3**) and **Lap**(**4**) allele frequencies remained effectively constant at Seatoun. Both these findings are consistent with the Long Island Sound model of selection. At all three locations, the **Lap**(**3** .3) genotype decreased in frequency From small to large mussels, whereas the **Lap**(**3**,4) genotype increased in frequency from small to large mussels. All other LAP genotypes occurred at low frequencies (< 0.10) at all three locations and showed no evidence of frequency change from small to large-size mussels nor evidence of clinal change among the three locations. These genotype frequency data possibly indicate that the **Lap**(**3**,3) genotype is at a selective disadvantage compared to the **Lap**(**3**,4) genotype at all three locations, and that this selective disadvantage is related to the extent of salinity variation which exists at each location. Further investigation is required before it can be determined if the Long Island Sound model of selection best describes the size-dependent and location-specific changes in LAP allele and genotype frequencies along this salinity gradient. Comparison of the population genetic structure at the LAP locus in 1995 and in 1997 revealed a profound change from heterozygote excesses to heterozygote deficiencies for all three M. galloprovincialis populations. The reason for the change is unknown, but the change indicates that population genetic structure at the LAP locus is highly variable in time, but consistent in spacer among these M. galloprovincialis populations.

L24 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
1992:165864 Document No.: BA93:88189. GENETICS OF LEUCINE AMINOPEPTIDASE IN APPLE. MANGANARIS A G; ALSTON F H. HORTICULTURE RES. INTERNATIONAL, EAST MALLING, WEST MALLING, MAIDSTONE, KENT ME19 6BJ, UK.. THEOR APPL GENET, (1992) 83 (3), 345-352. CODEN: THAGA6. ISSN: 0040-5752. Language: English.
AB Six zones of LAP activity were detected in apples, some of them tissue specific. Genetic studies in four of them revealed the presence of four games LAP-1, LAP-2, **LAP-3** and **LAP-4** with 4, 5, 4 and 4 alleles respectively including two null alleles. There were no big differences in allelic frequency within cultivars, selections,

rootstocks and Malus species. Close linkage was found between LAP-2 and resistance to mildew derived from 'White Angel'.

L24 ANSWER 3 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

86032925 EMBASE Document No.: 1986032925. A pharmacokinetic study of cefoperazone during percutaneous transhepatic cholangial catheterization. Suwa T.; Toyama N.; Hirakata S.; et al.. Japan. Japanese Journal of Antibiotics 38/8 (2033-2044) 1985.
CODEN: JJANAX. Pub. Country: Japan. Language: Japanese. Summary Language: English.

AB The metabolic fate of cefoperazone (CPZ) was studied in 19 cases undergoing percutaneous transhepatic cholangial catheterization (PTC-catheterization, PTCC) under various liver function conditions. 1. The peak of bile levels of CPZ immediately after PTCC differed greatly from one case to another, being 12.6-7,260 .mu.g/ml with a 1 g intravenous injection and 23.0-5,800 .mu.g/ml with a 2 g intravenous injection. 2. The ratio of the peak of bile level to the serum level immediately after PTCC showed the highest negative correlation with the serum total bilirubin level. It also showed a significant negative correlation with GOT, GPT, Al-P and **LAP**. **3**. The serum CPZ level and half-life showed no significant trend except half-life showed a significant correlation with **LAP**. **4**. The recovery rate in urine up to 12 hours was in the range of 14.8-93.6%, showing a significant correlation with the ratio of the peak of bile levels to the serum level and the date of liver function tests. 5. The bile level, serum level and recovery rate in urine at the time the bile outflow from the catheter has become constant after PTCC and during the course of PTCC showed a trend almost similar to that immediately after PTCC, there being no significant difference as to each parameter during the course of PTCC and immediately after PTCC. 6. In the cases in which the sample was collected by the cross-over technique, the ratio of the peak of bile levels to the serum level from immediately after PTCC compared to that during the course of PTCC increased in 2 cases and decreased in 6 cases. The 2 cases that showed an increase in the ratio were cases in which the serum total bilirubin level improved almost to normal. The findings above suggest that sufficient biliary decompression can improve the movement of CPZ into bile, despite the fact that the pharmacokinetics of CPZ is affected by the liver function, particularly serum total bilirubin level, that a decrease in the movement to bile and a compensatory increase in urinary excretion are observed in jaundice and disturbance of the liver function and that the ratio of the peak of bile level to the serum level decreases during the course of PTCC rather than immediately after PTCC in some cases.

L24 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1984:218334 Document No.: BA77:51318. ISOLATION AND CHARACTERIZATION OF AMINO PEPTIDASE MUTANTS OF SACCHAROMYCES-CEREVISIAE. TRUMBLY R J; BRADLEY G. CENT. LAB. RES., NEW YORK STATE DEP. HEALTH, ALBANY, N.Y. 12201.. J BACTERIOL, (1983) 156 (1), 36-48. CODEN: JOBAAY. ISSN: 0021-9193.
Language: English.

AB Mutants of S. cerevisiae, with decreased ability to hydrolyze leucine .beta.-naphthylamide, a chromogenic substrate for aminopeptidases, were isolated. The mutations were shown by starch gel electrophoresis to affect 1 of 4 aminopeptidases. Mutations affecting a given enzyme belong to a single complementation group. The 4 genes were symbolized lap1, lap2, lap3 and lap4, and the corresponding enzymes LAPI, LAPII, LAPIII and LAPIV. Both lap1 and lap4 were mapped to the left arm of chromosome XI; lap3 was mapped to the left arm of chromosome XIV. Strains possessing only 1 of the 4 leucine aminopeptidases (LAP) were constructed. Crude extracts from these strains were used to study the properties of individual enzymes. Dialysis against EDTA greatly reduced the activity of all LAP except LAPIII. Of cations tested, Co2+ was the most effective in restoring activity. Only LAPIV was reactived by Zn2+. LAPI was purified 331-fold and LAPII 126-fold from cell homogenates. Both purified enzymes had strong

activity on dipeptides and tripeptides. Activity levels of LAP were strongly dependent on growth stage in batch culture, with highest levels in early-stationary phase. Strains lacking all 4 LAP had lower growth rates than wild-type strains. The ability of leucine auxotrophs to grow on dipeptides and tripeptides containing leucine was not impaired in strains lacking all 4 LAP.

L24 ANSWER 5 OF 5 MEDLINE DUPLICATE 2
82012742 Document Number: 82012742. PubMed ID: 7278567. The heart rate, perceived exertion, and pace of the 1.5 mile run. Jackson A; Dishman R K; La Croix S; Patton R; Weinberg R. MEDICINE AND SCIENCE IN SPORTS AND EXERCISE, (1981) 13 (4) 224-8. Journal code: 8005433. ISSN: 0195-9131. Pub. country: United States. Language: English.

AB The logical validity of a 1.5-mile run as a measure of aerobic capacity, and the validity of Borg's laboratory model of perceived exertion (RPE) were examined in a field setting on a 440-yd cinder track. Performance time, heart rate (HR), and RPE were described for college-age males (N=67) instructed to achieve the lowest time possible during an "all-out" effort. Alpha and canonical factor analyses revealed three robust factors for performance times: 1) lap 1, 2) laps 2.5, 3) lap 6; two robust factors for HR: 1) **laps 3**-6, 2) laps 1 and 2; and four factors for RPE: 1) lap 6, 2) laps 1-3, 3) **laps 4** and 5, 4) first 220 yd of lap 1. Results indicated distinct pacing characteristics of an initial sprint, a stable speed reduction, and a finishing sprint. This pace was generally independent of Ss HR (r's, mean lap 1 = 0.09; mean laps 2-5 = 0.19, mean lap 6 = 0.21) and RPE (r's, mean lap 1 = -0.15; mean laps 2-5 = 0.12; mean lap 6 = 0.07), and in part these findings at least implicate confounding influences by anaerobic metabolism and Ss motivation on performance. This possibility was supported by the fact that 95% of performance variance could be accounted for by pace factors of the initial and finishing sprints. Both HR and RPE response followed a linear-like increase as a function of cumulative time and distance. However, only a small relationship between HR and RPE (r, mean = 0.16) was observed during the run, and the obtained correlations did not support a central RPE-control model based on cardiovascular stress.

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L29           0 L27 AND "LAP-3"

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L30          51 L27 AND ICE

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L31           4 L30 AND ANTIBODY

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L32 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
2001:781079 Document No. 135:348851 Albumin fusion proteins with therapeutic proteins for improved shelf-life. **Rosen, Craig A.**; Haseltine, William A. (Human Genome Sciences, Inc, USA). PCT Int. Appl. WO 2001079444 A2 20011025, 606 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US12013 20010412. PRIORITY: US 2000-PV229358 20000412; US 2000-PV199384 20000425; US 2000-PV256931 20001221.

AB The present invention encompasses fusion proteins of albumin with various therapeutic proteins. Therapeutic proteins may be stabilized to extend the shelf-life, and/or to retain the therapeutic protein's activity for extended periods of time in soln., in vitro and/or in vivo, by genetically or chem. fusing or conjugating the therapeutic protein to albumin or a fragment or variant of albumin. Use of albumin fusion proteins may also reduce the need to formulate the protein solns. with large excesses of carrier proteins to prevent loss of therapeutic proteins due to factors such as binding to the container. Nucleic acid mols. encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors contg. these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Thus, plasmid vectors are constructed in which DNA encoding the desired therapeutic protein may be inserted for expression of the albumin fusion proteins in yeast (pPPC0005) and mammalian cells (pC4:HSA). Yeast-derived signal sequences from Saccharomyces cerevisiae invertase SUC2 gene, or the stanniocalcin or native human serum albumin signal peptides, are used for secretion in yeast or mammalian systems, resp. Thus, the fusion product of human growth hormone with residues 1-387 of human serum albumin retains essentially intact biol. activity after 5 wk of incubation in tissue culture media at 37.degree., whereas recombinant human growth hormone used as control lost its biol. activity in the first week. Although the potency of the albumin fusion proteins is slightly lower than the unfused counterparts in rapid bioassays, their biol. stability results in much higher biol. activity in the longer term in vitro assay or in vivo assays. Addnl., the present invention encompasses pharmaceutical compns. comprising albumin fusion proteins and methods of treating, preventing, or ameliorating diseases, disorders or conditions using albumin fusion proteins of the invention.

L32 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS
1997:761953 Document No. 128:31833 Cloning of human interleukin-1.beta. converting enzyme-like apoptotic protease-6 and its diagnostic and therapeutic applications. Dixit, Vishva M.; **He, Wei-wu**; Ruben, Steven M.; Kikly, Kristine K. (Smithkline Beecham Corp., USA; Human Genome Sciences, Inc.; University of Michigan). Eur. Pat. Appl. EP 808904 A2 19971126, 44 pp. DESIGNATED STATES: R: BE, CH, DE, DK, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 1997-303397 19970519. PRIORITY: US 1996-17949 19960520; US 1996-20344 19960523; US 1996-18961 19960605.

AB Members of the **ICE**/Ced-3 gene family are likely effector components of the cell death machinery. A novel member of this family designated **ICE**-LAP-6 is provided. By phylogenetic anal., **ICE**-LAP6 is classified into the Ced-3 subfamily which includes Ced-3, Yama/CPP32/apopain, Mch2, and **ICE**-LAP3/Mch3/CMH-1.

Interestingly, **ICE**-LAP6 contains an active site QACGG pentapeptide, rather than the QACRG pentapeptide shared by other family members. Overexpression of **ICE**-LAP6 induces apoptosis in MCF7 breast carcinoma cells. More importantly, **ICE**-LAP6 is proteolytically processed into an active cysteine protease by granzyme B, an important component of cytotoxic T cell-mediated apoptosis. Once activated, **ICE**-LAP6 is able to cleave the death substrate poly(ADP-ribose) polymerase into signature apoptopic fragments. Also disclosed are methods for utilizing such **ICE** LAP-6 for the treatment of a susceptibility to viral infection, tumorogenesis, and to diseases and defects in the control embryogenesis and tissue homeostasis, and the nucleic acid sequences described may be employed in an assay for ascertaining such susceptibility. Agonists and antagonists of **ICE** LAP-6 may also be used to treat various disease states.

L32 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

1997:761853 Document No. 128:31110 Cloning and cDNA sequence of human interleukin-1.beta. converting enzyme-like apoptotic protease 7. Dixit, Vishva M.; Kikly, Kristine K.; Ni, Jian; **Rosen, Craig A.**; Ruben, Steven M. (Smithkline Beecham Corp., USA; Human Genome Sciences, Inc.; University of Michigan). Eur. Pat. Appl. EP 807686 A2 19971119, 48 pp. DESIGNATED STATES: R: BE, CH, DE, DK, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 1997-303203 19970512. PRIORITY: US 1996-17914 19960516; US 1996-17454 19960517; US 1996-19365 19960605.

AB Human interleukin-1.beta. converting enzyme apoptosis protease-7 (**ICE** LAP-7, or FLICE) polypeptides and DNA (RNA) encoding such **ICE** LAP-7 and a procedure for producing such polypeptides by recombinant techniques is disclosed. Also disclosed are methods for utilizing such **ICE** LAP-7 for the treatment of a susceptibility to viral infection, tumorogenesis, and to diseases and defects in the control embryogenesis and tissue homeostasis, and the nucleic acid sequences described above may be employed in an assay for ascertaining such susceptibility. Antagonists against such **ICE** LAP-7 and their use as a therapeutic to treat Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, septic shock, sepsis, stroke, chronic inflammation, acute inflammation, CNS inflammation, osteoporosis, ischemia reperfusion injury, cell death assocd. with cardiovascular disease, polycystic kidney disease, apoptosis of endothelial cells in cardiovascular disease, degenerative liver disease, MS, ALS, cerebellar degeneration, ischemic injury, myocardial infarction, AIDS, myelodysplastic syndromes, aplastic anemia, male pattern baldness, and head injury damage are also disclosed. Also disclosed are diagnostic assays for detecting diseases related to mutations in the nucleic acid sequences and altered concns. of the polypeptides. Also disclosed are diagnostic assays for detecting mutations in the polynucleotides encoding the interleukin-1.beta. converting enzyme apoptosis proteases and for detecting altered levels of the polypeptide in a host.

L32 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS

1996:142235 Document No. 124:200209 human interleukin-1.beta. converting enzyme like apoptosis protease-1 and 2 cDNA sequences and recombinant enzyme therapeutic uses. Wei, Wu He; Craig, A. Rosen; **Hastings, Gregg A.**; **Hudson, Peter L.**; Kirkness, Ewen F. (Human Genome Sciences, Inc., USA). PCT Int. Appl. WO 9600297 A1 19960104, 57 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, NZ, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US7127 19940623.

AB Disclosed are human interleukin-1.beta. converting enzyme like apoptosis proteases-1 and 2 and DNA (RNA) encoding such polypeptides. Also provided is a procedure for producing such polypeptides by recombinant techniques and **antibodies** and antagonists/inhibitors against such polypeptides. Also provided are methods of using the polypeptides, for example, as an antitumor agent, and antiviral agent, and

antibodies and antagonists/inhibitors against such polypeptides for example, for treating Alzheimer's disease, Parkinson's disease, rheumatoid arthritis and head injury.

=> s l27 and "QACRG"
L33 6 L27 AND "QACRG"

=> dup remove l33
PROCESSING COMPLETED FOR L33
L34 2 DUP REMOVE L33 (4 DUPLICATES REMOVED)

=> d l34 1-2 cbib abs

L34 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
1997:761953 Document No. 128:31833 Cloning of human interleukin-1.beta. converting enzyme-like apoptotic protease-6 and its diagnostic and therapeutic applications. Dixit, Vishva M.; **He, Wei-wu**; Ruben, Steven M.; Kikly, Kristine K. (Smithkline Beecham Corp., USA; Human Genome Sciences, Inc.; University of Michigan). Eur. Pat. Appl. EP 808904 A2 19971126, 44 pp. DESIGNATED STATES: R: BE, CH, DE, DK, FR, GB, IT, LI, NL. (English). CODEN: EPXXDW. APPLICATION: EP 1997-303397 19970519. PRIORITY: US 1996-17949 19960520; US 1996-20344 19960523; US 1996-18961 19960605.

AB Members of the ICE/Ced-3 gene family are likely effector components of the cell death machinery. A novel member of this family designated ICE-LAP-6 is provided. By phylogenetic anal., ICE-LAP6 is classified into the Ced-3 subfamily which includes Ced-3, Yama/CPP32/apopain, Mch2, and ICE-LAP3/Mch3/CMH-1. Interestingly, ICE-LAP6 contains an active site QACGG pentapeptide, rather than the **QACRG** pentapeptide shared by other family members. Overexpression of ICE-LAP6 induces apoptosis in MCF7 breast carcinoma cells. More importantly, ICE-LAP6 is proteolytically processed into an active cysteine protease by granzyme B, an important component of cytotoxic T cell-mediated apoptosis. Once activated, ICE-LAP6 is able to cleave the death substrate poly(ADP-ribose) polymerase into signature apoptopic fragments. Also disclosed are methods for utilizing such ICE LAP-6 for the treatment of a susceptibility to viral infection, tumorogenesis, and to diseases and defects in the control embryogenesis and tissue homeostasis, and the nucleic acid sequences described may be employed in an assay for ascertaining such susceptibility. Agonists and antagonists of ICE LAP-6 may also be used to treat various disease states.

L34 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
96279246 Document Number: 96279246. PubMed ID: 8663294. ICE-LAP6, a novel member of the ICE/Ced-3 gene family, is activated by the cytotoxic T cell protease granzyme B. Duan H; Orth K; Chinnaiyan A M; Poirier G G; Froelich C J; **He W W**; Dixit V M. (Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Jul 12) 271 (28) 16720-4. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Members of the ICE/Ced-3 gene family are likely effector components of the cell death machinery. Here, we characterize a novel member of this family designated ICE-LAP6. By phylogenetic analysis, ICE-LAP6 is classified into the Ced-3 subfamily which includes Ced-3, Yama/CPP32/apopain, Mch2, and ICE-LAP3/Mch3/CMH-1. Interestingly, ICE-LAP6 contains an active site QACGG pentapeptide, rather than the **QACRG** pentapeptide shared by other family members. Overexpression of ICE-LAP6 induces apoptosis in MCF7 breast carcinoma cells. More importantly, ICE-LAP6 is proteolytically processed into an active cysteine protease by granzyme B, an important component of cytotoxic T cell-mediated apoptosis. Once activated, ICE-LAP6 is able to cleave the death substrate poly(ADP-ribose) polymerase into signature apoptotic fragments.

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	141.14	141.35

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-6.82	-6.82

STN INTERNATIONAL LOGOFF AT 10:37:46 ON 03 DEC 2002